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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/738,378	12/17/2003	Francisco Javier Canada Vicinay	2798-1-001	7275

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EXAMINER	
UNDERDAHL, THANE E	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 09/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/738,378	VICINAY ET AL.	
	Examiner	Art Unit	
	Thane Underdahl	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *33,35 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-32 and 34, 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/9/05 and 8/17/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-38) in the reply filed on 7/31/2006 is acknowledged. The traversal is on the grounds that the inventions listed in groups I-III are a) not distinct and b) no search burden for the examination of the combined groups. This is not found persuasive because the product claimed in all three groups can be made by a materially different process disclosed in the art whose reference is repeated here: Rivera-Sagredo et al. Carbohydrate Research, 228(1) 1992. The examiner is burdened to search both relevant patent and patent applications as well as non-patent literature in the examination of the claims.

Also in response to the applicants comment that the election of species between *E. Coli* and *Kluyveramyces lactis* is incorrect, M.P.E.P. § 809.02 states the examiner may require an election of species between disclosed species and not only claimed species. Both microorganisms are disclosed together in paragraph 27 of the specification as sources for β-galactosidase which may be patentably distinct.

Therefore, the requirement is still deemed proper and is therefore made FINAL. However, upon initial search of the application, the election of species for Claim 1 step 5 of either acetone/methanol or acetone/water, and only this part of the election is withdrawn. The other 4 parts of the election remain.

Claims 33, 35, and 38 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 1-32 and 34, 36-39 have been considered on the merits in this office action.

DETAILED ACTION

Claim Objections

Claim 1(i) contains a typo "D-xylose 0-5-5%". For the purposes of examination the claim will read "0.5 to 5%". Please make the appropriate correction.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 20 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 20 teach that the reaction is stopped by cooling the reaction mixture to 0 °C. However the specification (Table I, paragraph 0049) indicates that the reaction continues down to –5 °C. Clarification is required.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 2, 3, 4, 21-24, 27-32, 34, 36, 37, 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyes et al (U.S. Patent # 5, 994, 092) in view of

Ponpipom et al. (U.S. Patent # 4, 228,274), and Crumpton et al. (Biochem J. 70(4) 1958, page 729) as supported by Chemindustry.com (www.chemindustry.com).

5. These claims are drawn to a method of production of 4-O-β-D-galactopyranosyl-D-xylose and purification from an enzymatic reaction between σ-nitrophenyl- β-galactopyranoside and xylose with β-galactosidase acting as the catalyst.

6. The patent of Reyes et al. teach a method for the preparation of 4-O-β-D-galactopyranosyl-D-xylose (4GPX) (See example 1, col 4). This method adds σ-nitrophenyl-β-galactopyranoside to xylose in buffered water at pH=7 with β-galactosidase from *E. coli* into a reaction mixture. The reaction mix is incubated for 5 hours and 45 mins at 25 °C. After that time the reaction is heated to 100°C for 10 mins and concentrated before being filtered on an activated carbon column with a water/ethanol gradient. This gradient isolates the 4-O- β-D-galactopyranosyl-D-xylose.

7. Claims 22-24 pertain to the amounts of D-xylose (claim 22), β-galactopyranoside (claim 23) and β-galactosidase (claim 24) added to the reaction solution. Reyes et al. already discusses the addition of these components in Example 1 in their patent (col 4 to col 5). Slight adjustments to the concentrations of the reaction mixture are rendered obvious in the absence of unexpected results or teachings of criticality since one of ordinary skill in the art would routinely optimize the reaction based on efficient use of enzyme and substrates to improve the cost to yield ratio.

8. Claims 27-31 pertain to the temperature conditions for the reaction of claim 1, which includes the following temperature ranges: constant temperature (claim 27), -5 °C to 40 °C (claim 28), lower than 0 °C (claim 29), -5 °C (claim 30), room temperature

(claim 31). Reyes et al. teach in Example 1 of their patent (col 4 to col 5) that the reaction can be performed at constant room temperature (25 °C). One of ordinary skill in the art would recognize that the hydrolysis of the substrate, σ-nitrophenyl-β-galactopyranoside by β-galactosidase will occur at any temperature in which the enzyme is active. This same artisan would also understand that the decrease of temperature will adjust the reaction rate. Therefore base on the time allotted for the reaction (i.e. performing the reaction overnight or over the lunch hour) one of ordinary skill in the art, through routine optimization would adjust the temperature accordingly.

Reyes et al. does not teach the crystallization of 4GPX. However crystallization is a common procedure for the purification of saccharides as taught by Ponpipom et al. who crystallized gycopyranosides in either cold water or acetone (col 3, line 50). Ponpipom et al. also teach that it is also possible to crystallize other glycopyranosides after a filtration step with diatomaceous silica (col 13, line 50) in solvents such as ethanol (col 10, line 68) or 2-propanone (col 13, line 44) or solvent mixtures such as ethyl acetate/ethyl ether (col 12, line 30). Diatomaceous silica is a synonym for Celite as supported by Chemindustry.com. Crumpton et al. teach that a disaccharide can be crystallized with aqueous acetone. With all these options available for the crystallization of saccharides, one of ordinary skill in the art would recognized that recrystallization is a common process for the isolation of saccharides and that the selection of solvent or mixture of solvents is a matter of routine optimization that depends on temperature, purity of the solvent and miscibility of the solvent systems used in the crystallization. Absent any teachings of criticality of the solvent selected and unexpected results one of

ordinary skill in the art would have reasonable expectation of success in crystallizing disaccharides with the current available art. Please see M.P.E.P. § 2144.05 (II) for further support.

Claims 1, 5, 6, and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyes et al (U.S. Patent # 5, 994, 092) in view of Ponpipom et al. (U.S. Patent # 4, 228,274), and Crumpton et al. (Biochem J. 70(4) 1958, page 729) as applied above and in further view of Wong-Madden et al. (U.S. Patent # 5,770,405) and Dahmen et al. (U.S. Patent # 4,675,392).

These claims pertain to a method of isolation of 4GPX via a solid-liquid extraction using a column with an eluent and gradient of water/isopropanol.

Reyes et al., Ponpipom et al., and Crumpton et al. teach the enzyme assisted synthesis and purification via and activated carbon column and crystallization of 4GPX as detailed above.

Reyes et al. does teach the use of a water/ethanol gradient to elute 4GPX from an activated carbon column but not water/isopropanol as limited in claims 5 and 6. However Wong-Madden et al. (U.S. Patent # 5, 770,405) shows that solvent mixes of water/isopropanol/ethanol are suitable for the separation of oligosaccharides (col 12, table 2). It would be obvious to one skilled in the art to replace ethanol in the method of Reyes et al. with isopropanol since Wong-Madden et al. shows that these act as art defined equivalents for the separation of saccharides.

Claims 16-19 discuss the purification of 4GPX on an activated carbon column which is taught by Reyes et al. (Example 1, col 5, line 3) who uses a solvent gradient of

water/ethanol to elute 4GPX. As mentioned above Wong-Madden et al. shows that it is obvious to replace the water/ethanol gradient with an isopropanol/water solvent mixture. However neither directly teaches the specifics of the solvent gradient in claims 17 nor the amount of activated carbon to use in claim 18. These items are result effective variables optimized by routine experimentation by one or ordinary skilled in the art. The average skilled artisan would recognize that the solvent gradient will depend on the size of the column particles, the length and width of the column as well as the time allotted for the separation. The amount of activated carbon to use will depend on the perceived yield of 4GPX and the loading amounts of reaction mixture the column can bear to separate.

9. Claims 1, 7-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyes et al (U.S. Patent # 5, 994, 092) in view of Ponpipom et al. (U.S. Patent # 4, 228,274), Crumpton et al. (Biochem J. 70(4) 1958, page 729) Wong-Madden et al. (U.S. Patent # 5,770,405) and Dahmen et al. (U.S. Patent # 4,675,392) as applied above and in further view of Rao et al. (Qual. Plant. -Pl.Fds.hum.Nutr. XXVIII 4:293-303, 1979).

10. These claims pertain to the method of extracting the 4GPX with celite and a Soxhlet extractor.

11. Claim 7 depends from claim 1 and limits the additional purification of the disaccharide to include the addition of celite and to the reaction mixture and extraction of the disaccharide with a Soxhlet extractor. Neither of these are taught by Reyes et al. However, the use of Soxhlet extractors and celite are known in the art as methods to

purify saccharides as taught by Rao et al. (page 294, 3rd paragraph and 295 1st paragraph respectively) as well as previously mentions by Ponpipom et al. above. Rao et al. also uses a non-polar/polar solvent mix of chloroform and methanol. However one of ordinary skill in the art would recognize that the main requirement for a solvent for Soxhlet extraction is that the compound be soluble in the hot solvent. It would be obvious to one skilled in the art to select other solvents or solvent mixes, known to dissolve saccharides such as those listed above by Ponpipom et al., or by those listed by Dahmen et al. who lists multiple solvents that other disaccharides are soluble in such as ethyl acetate (col 13, line 67) or solvent systems such as isooctane/ethyl acetate (col 14, line 42) for use in Soxhlet extraction. Again it would be a matter of routine optimization by the artisan to select solvents known in the art that dissolved saccharides (see M.P.E.P. § 2144.05 (II)) for Soxhlet extraction and absent any evidence to the criticality of solvent selection for the extraction or teaching of an unexpected result, one of ordinary skill in the art would have a reasonable expectation of success.

The amount of solvent used to elute the disaccharide from celite is also a matter of routine optimization by one of skill in the art. The volume of solvent to remove the disaccharide would depend on the size of the celite particles, the purity of the solvent and the temperature of the solvent and the amount of disaccharide absorbed on the celite.

Also a matter of routine optimization is the amount of celite to use in the extraction of the disaccharide. One of ordinary skill in the art would recognize that overloading the column would not accomplish the goal of purifying the disaccharide.

Therefore this artisan would know the loading parameters of the celite or carbon-celite used in the experiment. He/she would also recognize that the loading amount of celite necessary for the purification would depend on the size and surface area of the celite particles. The skilled artisan would recognize that he/she must use the necessary amount of celite to purify the disaccharide base on the prospective yield. Larger reaction batches would require larger amounts of celite.

Claims 11 and 15 limit that the carbon in the activated carbon-celite column must be deactivated with HCl. One of ordinary skill in the art would recognize that the procedure for deactivating the column is a matter or routine optimization that would depend on the amount of the activated carbon in the column and the size of the column and recommendations from the manufacture. It would also be dependant on the size and surface area of the carbon particles since this would determine how many theoretical plates were available for the adsorption and separation of the disaccharide.

12. Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reyes et al (U.S. Patent # 5, 994, 092) in view of Ponpipom et al. (U.S. Patent # 4, 228,274), Crumpton et al. (Biochem J. 70(4) 1958, page 729), Dahmen et al. (U.S. Patent # 4,675,392), Rao et al. (Qual. Plant-Pl.Fds.hum. Nutr. XXVIII, 4: 1979, page 293) and Wong-Madden et al. (U.S. Patent # 5,770,405) in further view of Gabelsberger et al (FEMS Letters, 109(2-3), page 131, 1993), Fujimoto et al. (Glycogonjugate Journal 15, page 155, 1998) and Yoshitake et al.(Eur. J. Biochem. 101, page 395, 1979).

13. These claims are drawn to the addition of cosolvents DMF, DMSO and dioxane to the reaction medium in the method of claim 1.

14. Reyes et al. and references listed above teach the method of claim 1 from which 25 and 26 depend. Reyes et al. teach the use of a phosphate buffer as the reaction solution but not with a cosolvent. However three other references that involve reactions using β-galactosidase use DMF (Fujimoto et al., page 157, col 1, 1st and 3rd paragraphs), DMSO (Gabelsberger et al. page 133, col 1, 1st paragraph) and dioxane (Yoshitake et al., page 396, col 2 line 1) in the formulation of their phosphate buffer. All three of these reactions use the organic solvent/phosphate buffer system successfully with β-galactosidase to hydrolyze a substrate. It would have been obvious to someone skilled in the art to use either of the three solvents in the phosphate buffer in the method of Reyes et al. Since all three share the same goal of Reyes of hydrolyzing a substrate with β-galactosidase. Each provides a reasonable expectation of success since each accomplishes the hydrolysis of their substrate using their phosphate buffer cosolvent.

15. The amount of the cosolvent ranges from 20% in Fujimoto et al. to 2% in Yoshitake et al. One of ordinary skill in the art would recognize that the amount of DMSO is an optimizable parameter and that the amount of solvent in the phosphate buffer would depend on the amount of enzymes in the solution along with the solubility tolerance of the substrate in the buffer as the co-solvent increases or decreases. Therefore claim 26 is rendered obvious since one of ordinary skill in the art would meet the limitation through routine optimization of the co-solvent in the reaction mixture.

In summary no claims, as written, are allowed for this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571) 272-9042. The examiner can normally be reached on 8:00 to 17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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